BIRTH DEFECT RISK FACTOR SERIES: ORAL CLEFTS

DEFINITION

The two main types of oral clefts are cleft lip and cleft palate. Cleft lip is the congenital failure of the maxillary and median nasal processes to fuse, forming a groove or fissure in the lip. Cleft palate is the congenital failure of the palate to fuse properly, forming a grooved depression or fissure in the roof of the mouth. Cleft lip and cleft palate can occur alone or together. For etiologic reasons, cleft lip with or without cleft palate are often grouped together and isolated cleft palate is kept separate. Oral clefts frequently occur with a wide range of chromosomal abnormalities and syndromes (trisomy 21, trisomy 13, amniotic band anomalad, Fryns syndrome, Meckel syndrome, Stickler syndrome, Treacher Collins syndrome, van der Woude syndrome, Velocardiofacial syndrome, etc.) (Torfs and Christianson, 1998; Kallen et al., 1996; Stoll et al., 1991).

Oral clefts can be detected by antenatal ultrasound, although the prenatal detection rate is relatively low. Because of prenatal detection of oral clefts and/or other birth defects, a few fetuses with oral clefts are electively terminated in areas where prenatal detection and elective termination are available (Sohan et al., 2001; Clementi et al., 2000; Forrester et al., 1998; Stoll et al., 1995; Stoll et al., 1992; Stoll et al., 1991).

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

There are **racial/ethnic** differences in risk for oral clefts. Asians generally have been reported to have the highest risk, followed by whites, Hispanics, and African-Americans (Das et al., 1995; Leck and Lancashire, 1995). In one study, risk of cleft lip with cleft palate was higher among infants of Vietnamese mothers when compared with infants of non-Hispanic white mothers, while there was no difference between the two populations for risk of cleft palate alone (Shaw et al., 2002). Several investigations have reported oral cleft rates to be highest among Native Americans (Croen et al., 1998; Chavez et al., 1988; Lowry et al., 1986). Among Asians, the risk for oral clefts is higher among Far East Asians (Japanese, Chinese, Korean) and Filipinos than Pacific Islanders (Croen et al., 1998; Yoon et al., 1997).

In part because of the racial/ethnic differences in oral cleft prevalence, **genetic factors** are believed to account for some of the defects. There is evidence of two main types of cleft lip and palate in whites (Ardinger et al., 1989; Chung et al., 1986; Johnston et al., 1989). One type is controlled by a single gene, which may code for a **transforming growth factor-alpha (TGFa)** variant. The other type is multifactorial in nature. Asians do not appear to have a major gene etiology for oral clefts (Ardinger et al., 1989; Chung et al., 1986; Chung et al., 1987; Johnston et al., 1989). Polymorphisms in the **microsomal epoxide hydrolase (EPHX1)**, **glutathione S-transferase (GSTM1)**, **BCL1**, **cytochrome P450 1A1 (CYP1A1)**, and **glutathione S-transferase theta 1-1 (GSTT1)** genes were not found to be associated with risk for cleft lip with or without cleft palate (Rittler et al., 2001; van Rooij et al., 2001). Neither does mutations in the **Sonic Hedgehog** gene appear to influence oral cleft risk (Orioli et al., 2002).

Several studies have reported increased risk of oral clefts with increased **maternal age** (Shaw et al., 1991). However, these studies generally included a small number of cases. Several other studies failed to identify a maternal age risk for cleft lip and palate (Hollier et al., 2000; Baird et al., 1994; Stoll et al., 1991). Oral cleft risk may also be higher with both the lowest and the highest **paternal age** groups (McIntosh et al., 1995) or may not be associated with paternal age (Stoll et al., 1991).

Demographic factors not considered to affect risk for oral clefts include **season** (Stoll et al., 1991; Castilla et al., 1990; Bound et al., 1989), **geographic location** (Christensen et al., 1995; Stoll et al., 1991**)**, and

parity (Shaw et al., 1991; Stoll et al., 1991). One investigation did report risk of cleft lip, but not cleft palate, to be increased with higher **altitude** (Castilla et al., 1999).

Infant sex influences the risk for oral clefts. Males are more likely than females to have a cleft lip with or without cleft palate, while females are at slightly greater risk for isolated cleft palate (Ko et al., 2001; Lary and Paulozzi, 2001; Natsume et al., 2000; Riley et al., 1998; Das et al., 1995; Stoll and EUROCAT Working Group, 1995; Lowry et al., 1986; Owens et al., 1985; Shaw et al., 1991; Stoll et al., 1991). Oral cleft rates do not appear to be affected by **plurality** but are higher with lower **birth weight** (Riley et al., 1998; Doyle et al., 1991; Mili et al., 1991; Ramos-Arroyo, 1991; Stoll et al., 1991; Kallen, 1986) and **prematurity** (Rasmussen et al., 2001). However, one study found increased risk for cleft lip with or without cleft palate in multiple gestation pregnancies, but not for cleft palate alone, (Mastroiacovo et al., 1999). Oral clefts have been associated with **intrauterine growth retardation** (Khoury et al., 1988). There is no association between oral clefts and **macrosomia** (Lapunzina et al., 2002; Waller et al., 2001).

Consanguinity may increase risk of oral clefts (Rittler et al., 2001; Stoltenberg et al., 1997; Stoll et al., 1991).

FACTORS IN LIFESTYLE OR ENVIRONMENT

Various studies have suggested that oral cleft risk increases with lower **socioeconomic status (SES)**, although other studies failed to support this (Vrijheid et al., 2000). **Education** does not appear to influence oral cleft rates (Stoll et al., 1991).

Increased risk of oral clefts has been linked with maternal occupations of **leather worker**, **hairdresser**, and **housekeeper** and exposure to **aliphatic aldehydes**, **glycol ethers**, **aliphatic acids**, **glycol ethers**, **biocides**, **lead**, **antineoplastic drugs**, **trichloroethylene**, and **aliphatic solvents** (Cordier et al., 2001; Lorente et al., 2000a; Bianchi et al., 1997; Cordier et al., 1997; Laumon et al., 1996). One investigation identified no significant association between **maternal nursing occupation** and oral cleft risk (Matte et al., 1993). The **water contaminants** trichloroethylene, **tetrachloroethylene**, and **total dichloroethylenes** have been associated with elevated oral cleft rates (Bove et al., 1995), although several studies observed no association between oral clefts and water chlorination (Jaakkola et al., 2001; Kallen and Robert, 2000). One investigation found no association between total **trihalomethanes** and oral clefts (Dodds et al., 1999), and another study found no relationship between **chloroform** or **bromodichloromethane** in drinking water and risk of cleft defects (Dodds and King, 2001).

Maternal occupational exposure to **organic solvents** such as xylene, toluene, and acetone have been reported to increase the rate of cleft lip (Wyszynski and Beaty, 1996; Holmberg et al., 1982). Maternal **agriculture work**, home proximity to agriculture, and exposure to **pesticides** has been reported to increase rates of oral clefts (Garcia et al., 1999; Wyszynski and Beaty, 1996; Nurminen et al., 1995; Gordon and Shy, 1981); however, other studies failed to find a link between pesticides and oral cleft risk (Shaw et al., 1999a; Kristensen et al., 1997; Wyszynski and Beaty, 1996). Paternal agricultural work and pesticide exposure was not found to affect oral cleft rates (Garcia et al., 1999). One study failed to find any link between parental occupational exposure to **lead** and oral cleft risk. However, the number of cases in the study was small, and the measure of lead exposure was based on census records (Irgens et al., 1998). Another investigation reported increased risk of oral clefts, mainly cleft lip, with environmental lead exposure; the risk declined with decreasing environmental lead levels (Vincenti et al., 2001).

Living in proximity to **hazardous waste** sites does not appear to increase risk for cleft lip and palate (Dolk et al., 1998; Croen et al., 1997). An investigation failed to identify any significant association between oral clefts and proximity to various types of **industry** (Castilla et al., 2000). One study reported a negative association between isolated cleft palate risk and maternal, but not paternal, occupational exposure to **electromagnetic fields**; Ther was no association between cleft lip risk and maternal or paternal

occupation exposure to electromagnetic fields. However, exposure was based on linkage to census data and exposure assessments by an expert panel (Blaasaas et al., 2002).

One study that examined the relationship between ambient air pollution and isolated oral clefts found no clear association between the defects and **carbon monoxide**, **nitrogen dioxide**, **ozone**, or **PM_{10}** (Ritz et al., 2002).

Research has reported no impact of **paternal occupations** of **painter**, **printer**, **welder**, **forestry**, **driver**, **sales**, or **electric occupation** on oral cleft risk (Irgens et al., 2000). One investigation reported no association between paternal **ionizing radiation** exposure in the nuclear industry and oral cleft rates (Doyle et al., 2000).

Several studies have reported **maternal psychosocial or emotional stress** during pregnancy may increase risk of having an infant with an oral cleft (Hansen et al., 2000; Carmichael and Shaw, 2000). One hypothesis is that this that the oral clefts are induced because of maternal production of **cortisone**, a stress hormone. However, investigations of a possible relationship between cortisone and **corticosteroids** in pregnancy and oral clefts are mixed (Park-Wyllie et al., 2000; Kallen et al., 1999; Rodriguez Pinilla and Martinez Frias, 1998; Czeizel and Rockenbauer, 1997; Robert et al., 1994).

The **anticonvulsant medications** such as **phenobarbital** and **methyphenobarbital** have been documented to increase incidence of oral clefts (Arpino et al., 2000; Wyszynski and Beaty, 1996; Dravet et al., 1992; Dansky and Finnell, 1991; Hanson et al., 1976). However, there is some question as to whether this increase is due to the medications or the underlying **epilepsy** (Wyszynski and Beaty, 1996), although one study found no association between epilepsy and oral clefts (Stoll et al., 1991). **Trimethadione**, **valproate**, **dilantin**, **isotretinoin**, and **aminopterin** have been identified as potential causative factors for oral clefts (Ardinger et al., 1988; Benke, 1984; Hanson et al., 1984; Warkany, 1978; Feldman et al., 1977; Zackai et al., 1975; Meadow, 1970). **Diazepam (Valium)** and **Bendectin** have not been found to increase the rate of oral clefts (Rosenberg et al., 1983; Mitchell et al., 1981). Maternal use of the **benzodiazepines** nitrazepam, medazepam, tofisopam, alprazolum, and clonazepam have not been associated with oral cleft risk (Eros et al., 2002). An investigation noted increased risk of cleft lip with or without cleft palate with maternal use of **co-trimoxazole (sulfamethoxazole and trimethoprim, Bactrim, Septrin, Septra, Sumetrolim)**; however, exposure to the medication was not higher during the critical period of defect formation (Czeizel, 1990). Oral clefts do not appear to be associated with maternal use of cough medicines containing **dextromethorphan** (Martinez-Frias and Rodriguez-Pinilla, 2001), **cephalosporin antibiotics** (Czeizel et al., 2001a), **nalidixic acid** (Czeizel et al., 2001b), **augmentin** (Czeizel et al., 2001c), or **calcium channel blockers** (Sorensen et al., 2001). Investigations have observed increased rates of oral clefts with maternal use of **oxytetracycline** and **ampicillin** during pregnancy (Czeizel and Rockenbauer, 2000; Czeizel et al., 2001d). Cleft palate, and possibly cleft lip, may be associated with use of **misoprostol**, a synthetic postaglandin used for elective termination (Orioli and Castilla, 2000).

Maternal **common cold** in the first trimester of pregnancy has been reported to increase risk of cleft lip (Zhang and Cai, 1993). Maternal **hyperthyroidism** and **hypothyroidism** do not appear to influence risk of oral clefts (Khoury et al., 1989a), although several investigations reported higher rates of oral clefts among mothers who had hypertension (Ko et al., 2001; Stoll et al., 1991). Maternal **fever** and **influenza** and exposure to **radiation** do not seem to be associated with oral clefts (Stoll et al., 1991). Maternal **urinary tract infection** has not been linked with oral cleft risk (Beaty et al., 2001). Higher rates of oral clefts have been reported with maternal **diabetes** (Aberg et al., 2001; Ko et al., 2001; Spilson et al., 2001; Janssen et al., 1996; Becerra et al., 1990), although one investigation reported no such association (Ramos-Arroyo et al., 1992). One study noted increased rates of infants with oral clefts born to women with **obesity** but who were not diabetic (Moore et al., 2000).

Maternal smoking has been linked to cleft lip and palate in their children; however, the studies have not been conclusive (Beaty et al., 2001; Ko et al., 2001; Mitchell et al., 2001; Lorente et al., 2000b; Lieff et al., 1999; Werler, 1997; Stoll et al., 1991; Van Den Eeden et al., 1990; Werler et al., 1990; Khoury et al., 1989b; Khoury et al., 1987; Shiono et al., 1986; Christianson, 1980; Erikson et al., 1979). **Alcohol** has also been presented as increasing the risk of oral clefts (ko et al., 2001; Lorente et al., 2000b; Shaw and Lammer, 1999; Munger et al., 1996; Werler et al., 1991; Hassler and Moran, 1986; Streissguth et al., 1980; Clarren and Smith, 1978), although not all studies have reported this association (Beaty et al., 2001; Mitchell et al., 2001). **Caffeine** has not been linked to oral cleft risk (Rosenberg et al., 1982). One investigation found mothers of infants with oral clefts drank less alcohol and less **coffee** during early pregnancy than mothers of normal infants (Natsume et al., 2000). Maternal **recreation drug** use has not been reported to affect oral cleft rates (Beaty et al., 2001).

Periconceptional use of **electric bed-heating devices** (electric blankets, bed warmers, and heated waterbeds) does not appear to affect risk for oral clefts (Shaw et al., 1999b; Dlugosz et al., 1992).

Nutrition has been suggested as playing a role in the risk of oral clefts. Maternal **multivitamin** use has been found to result in a reduction in cleft palate and cleft lip risk (Itikala et al., 2001; Loffredo et al., 2001; Werler et al., 1999), although not all investigations have reported this association (Beaty et al., 2001). Several studies have reported decreased rates of cleft lip and palate with **folic acid** use (Czeizel et al., 1996; Mulinare et al., 1995; Munger et al., 1997; Shaw et al., 1995; Tolarova and Harris, 1995), while other studies have failed to find such an effect (Hays et al., 1996). Some ambiguity of the studies may be explained by recent research that found oral cleft risk can be reduced only by high doses of folic acid consumed at the time of lip and palate formation (Czeizel et al., 1999). Data suggest that **folic acid antagonists** such as **dihydrofolate reductase inhibitors,** antiepileptic medications, and **co-trimoxazole** increase risk of oral clefts (Czeizel et al., 2001e; Hernandez-Diaz et al., 2000; Czeizel, 1990). **Vitamin B-12** and **zinc** have also been reported to reduce risk of oral clefts (Munger et al., 1997).

In general, environmental factors are considered much less important than genetic factors in the etiology of oral clefts (Christensen et al., 1995; Fraser, 1970). However, genes and environment may operate in combination to affect oral cleft risk. Mutations in the **methylenetetrahydrofolate reductase (MTHFR) gene** have been offered as potential risk factors for oral clefts, although the results of studies have been inconsistent (Beaty et al., 2002; Martinelli et al., 2001; Mills et al., 1999; Gaspar et al., 1999; Shaw et al., 1998a). Certain mutations in the **transforming growth factor-alpha (TGFa) gene** and smoking or multivitamin use may affect oral cleft risk (Christensen et al., 1999; Shaw et al., 1998b; Beaty et al., 1997; Shaw et al., 1996; Hwang et al., 1995), although not all investigation had reported associations with these genes (Beaty et al., 2002; Beaty et al., 2001). Mutations in **transforming growth factor-beta (TGFb)** and **Msh homeobox homolog 1 (MSX1) genes** have been associated with increased risk of cleft palate (Beaty et al., 2002; Beaty et al., 2001; Mitchell et al., 2001). Maternal smoking in the presence of the GSTT1-null genotype has been associated with increased risk of oral clefts (van Rooij et al., 2001). TGFb and MSX1 may interact with maternal smoking or alcohol to influence risk of oral clefts (Romitti et al., 1999), although the results of investigations into this interaction have been inconsistent (Mitchell et al., 2001).

REFERENCES

Aberg A, Westbom L, Kallen B. Congenital malformations among infants whose mothers had gestational diabetes or preexisting diabetes. Early Hum Dev 2001;61:85-95.

Ardinger HH, Atkin JF, Blackston RD, Elsas LJ, Clarren SK, Livingstone S, Flannery DB, Pellock JM, Harrod MJ, Lammer EJ, et al. Verification of the fetal valproate syndrome phenotype. Am J Med Genet 1988;29:171-185.

Ardinger HH, Buetow KH, Bell GI, Bardach J, VanDemark DR, Murray JC. Association of genetic variation of the transforming growth factor-alpha gene with cleft lip and palate. Am J Hum Genet 1989;45:348-353.

Arpino C, Brescianini S, Robert E, Castilla EE, Cocchi G, Cornel MC, de Vigan C, Lancaster PA, Merlob P, Sumiyoshi Y, Zampino G, Renzi C, Rosano A, Mastroiacovo P. Teratogenic effects of antiepileptic drugs: use of an international database on malformations and drug exposure. Epilepsia 2000;41:1436-1443.

Baird PA, Sadovnick AD, Yee IM. Maternal age and oral cleft malformations: Data from a population-based series of 576,815 consecutive livebirths. Teratology 1994;49:448-51.

Beaty TH, Maestri NE, Hetmanski JB, Wyszynski DF, Vanderkolk CA, Simpson JC, McIntosh I, Smith EA, Zeiger JS, Raymond GV, Panny SR, Tifft CJ, Lewanda AF, Cristion CA, Wulfsberg EA. Testing for interaction between maternal smoking and TGFA genotype among oral cleft cases born in Maryland 1992-1996. Cleft Palate Craniofac J 1997;34:447-454.

Beaty TH, Wang H, Hetmanski JB, Fan YT, Zeiger JS, Liang KY, Chiu YF, Vanderkolk CA, Seifert KC, Wulfsberg EA, Raymond G, Panny SR, McIntosh I. A case-control study of nonsyndromic oral clefts in Maryland. Ann Epidemiol 2001;11:434-442.

Beaty TH, Hetmanski JB, Zeiger JS, Fan YT, Liang KY, VanderKolk CA, McIntosh I. Testing candidate genes for non-syndromic oral clefts using a case-parent trio design. Genet Epidemiol 2002;22:1-11.

Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. Pediatrics 1990;85:1-9.

Benke PJ. The isotretinoin teratogen syndrome. JAMA 1984;251:3267-3269.

Bianchi F, Cianciulli D, Pierini A, Seniori Costantini A. Congenital malformations and maternal occupation: a registry based case-control study. Occup Environ Med 1997;54:223-228.

Blaasaas KG, Tynes T, Irgens A, Lie RT. Risk of birth defects by parental occupational exposure to 50 Hz electromagnetic fields: a population based study. Occup Environ Med 2002;59:92-97.

Bound JP, Harvey PW, Francis BJ. Seasonal prevalence of major congenital malformations in the Fylde of Lancashire 1957-1981. J Epidemiol Community Health 1989;43:330-342.

Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. Public drinking water contamination and birth outcomes. Am J Epidemiol 1995;141:850-862.

Carmichael SL, Shaw GM. Maternal life event stress and congenital anomalies. Epidemiology 2000;11:30-35.

Castilla EE, Campana H, Camelo JS. Economic activity and congenital anomalies: an ecologic study in Argentina. Environ Health Perspect 2000;108:193-197.

Castilla EE, Lopez-Camelo JS, Campana H. Altitude as a risk factor for congenital anomalies. Am J Med Genet 1999;86:9-14.

Castilla EE, Orioli IM, Lugarinho R, Dutra GP, Lopez-Camelo JS, Campana HE, Spagnolo A, Mastroiacovo P. Monthly and seasonal variations in the frequency of congenital anomalies. Int J Epidemiol 1990;19:399-404.

Chavez GF, Cordero JF, Becerra JE. Leading major congenital malformations among minority groups in the United States, 1981-1986. Mor Mortal Wkly Rep CDC Surveill Summ 1988;37:17-24.

Christianson RE. The relationship between maternal smoking and the incidence of congenital anomalies. Am J Epidemiol 1980;112:684-695.

Christensen K, Schmidt MM, Veth M, Olsen J. Absence of an environmental effect on the recurrence of facial-cleft defects. N Engl J Med 1995;333:161-164.

Christensen K, Olsen J, Norgaard-Pedersen B, Basso O, Stovring H, Milhollin-Johnson L, Murray JC. Oral clefts, transforming growth factor alpha gene variants, and maternal smoking: a population-based case-control study in Denmark, 1991-1994. Am J Epidemiol 1999;149:248-255.

Chung CS, Bixler D, Watanabe T, Koguchi H, Fogh-Andersen P. Segregation analysis of cleft lip with or without cleft palate: a comparison of Danish and Japanese data. Am J Hum Genet 1986;39:603-611.

Chung CS, Mi MP, Beechert AM. Genetic epidemiology of cleft lip with or without cleft palate in the population of Hawaii. Genet

Epidemiol 1987;4:415-423.

Clarren SK, Smith DW. The fetal alcohol syndrome. N Engl J Med 1978;298:1063-1067.

Clementi M, Tenconi R, Bianchi F, Stoll C. Evaluation of prenatal diagnosis of cleft lip with or without cleft palate and cleft palate by ultrasound: experience from 20 European registries. Prenat Diagn 2000;20:870-875.

Cordier S, Szabova E, Fevotte J, Bergeret A, Plackova S, Mandereau L. Congenital malformations and maternal exposure to glycol ethers in the Slovak Republic. Epidemiology 2001;12:592-593.

Cordier S, Bergeret A, Goujard J, Ha MC, Ayme S, Bianchi F, Calzolari E, De Walle HE, Knill-Jones R, Candela S, Dale I, Dananche B, de Vigan C, Fevotte J, Kiel G, Mandereau L. Congenital malformations and maternal occupational exposure to glycol ethers. Epidemiology 1997;8:355-363.

Croen LA, Shaw GM, Wasserman CR, Tolarova MM. Racial and ethnic variations in the prevalence of orofacial clefts in California, 1983-1992. Am J Med Genet 1998;79:42-47.

Croen LA, Shaw GM, Sanbonmatsu L, Selvin S, Buffler PA. Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations. Epidemiology 1997;8:347-354.

Czeizel A. A case-control analysis of the teratogenic effects of co-trimoxazole. Reprod Toxicol 1990;4:305-313.

Czeizel AE, Toth M, Rockenbauer M. Population-based case control study of folic acid supplementation during pregnancy. Teratology 1996;53:345-351.

Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology 1997;56:335-340.

Czeizel AE, Timar L, Sarkozi A. Dose-dependent effect of folic acid on the prevention of orofacial clefts. Pediatrics 1999;104:e66.

Czeizel AE, Rockenbauer M. A population-based case-control teratologic study of oral oxytetracycline treatment during pregnancy. Eur J Obstet Gynecol Reprod Biol 2000;88:27-33.

Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Use of cephalosporins during pregnancy and in the presence of congenital abnormalities: a population-based, case-control study. Am J Obstet Gynecol 2001a;184:1289-1296.

Czeizel AE, Sorensen HT, Rockenbauer M, Olsen J. A population-based case-control teratologic study of nalidixic acid. Int J Gynaecol Obstet 2001b;73:221-228.

Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Augmentin treatment during pregnancy and the prevalence of congenital abnormalities. A population-based case-control teratologic study. Eur J Obstet Gynecol Reprod Biol 2001c;97:188-192.

Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. A population-based case-control teratologic study of ampicillin treatment during pregnancy. Am J Obstet Gynecol 2001d;185:140-147.

Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. Reprod Toxicol 2001e;15:637-646.

Dansky LV, Finnell RH. Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades; 2: Human studies. Reprod Toxicol 1991;5:301-335.

Das SK, Runnels RS, Smith JC, Cohly HH. Epidemiology of cleft lip and cleft palate in Mississippi. South Med J 1995;88:437-442.

Dlugosz L, Vena J, Byers T, Sever L, Bracken M, Marshall E. Congenital defects and electric bed heating in New York State: a register-based case-control study. Am J Epidemiol 1992;135:1000-1011.

Dodds L, King W, Woolcott C, Pole J. Trihalomethanes in public water supplies and adverse birth outcomes. Epidemiology 1999;10:233-237.

Dodds L, King WD. Relation between trihalomethane compounds and birth defects. Occup Environ Med 2001;58:443-446.

Dolk H, Vrijheid M, Armstrong B, Abramsky L, Bianchi F, Garne E, Nelen V, Robert E, Scott JE, Stone D, Tenconi R. Risk of congenital

anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study. Lancet 1998;352:423-427.

Doyle P, Maconochie N, Roman E, Davies G, Smith PG, Beral V. Fetal death and congenital malformation in babies born to nuclear industry employees: report from the nuclear industry family study. Lancet 2000;356:1293-1299.

Doyle PE, Beral V, Botting B, Wale CJ. Congenital malformations in twins in England and Wales. J Epidemiol Community Health 1991;45:43-48.

Dravet C, Julian C, Legras C, Magaudda A, Guerrini R, Genton P, Soulayrol S, Giraud N, Mesdjian E, Trentin G, et al. Epilepsy, antiepileptic drugs, and malformations in children of women with epilepsy: a French prospective cohort study. Neurology 1992;42:75-82.

Erikson A, Kallen B, Westerholm P. Cigarette smoking as an etiologic factor in cleft lip and palate. Am J Obstet Gynecol 1979;135:346-351.

Eros E, Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. A population-based case-control teratologic study of nitrazepam, medazepam, tofisopam, alprazolum and clonazepam treatment during pregnancy. Eur J Obstet Gynecol Reprod Biol 2002;101:147-154.

Feldman GL, Weaver DD, Lovrien EW. The fetal trimethadione syndromes. Am J Dis Child 1977;131:1389-1392.

Forrester MB, Merz RD, Yoon PW. Impact of prenatal diagnosis and elective termination on the prevalence of selected birth defects in Hawaii. Am J Epidemiol 1998;148:1206-1211.

Fraser FC. The genetics of cleft lip and palate. Am J Hum Genet 1970;22:336-352.

Garcia AM, Fletcher T, Benavides FG, Orts E. Parental agricultural work and selected congenital malformations. Am J Epidemiol 1999;149:64-74.

Gaspar DA, Pavanello RC, Zatz M, Passos-Bueno MR, Andre M, Steman S, Wyszynski DF, Matiolli SR. Role of the C677T polymorphism at the MTHFR gene on risk to nonsyndromic cleft lip with/without cleft palate: results from a case-control study in Brazil. Am J Med Genet 1999;87:197-9.

Gordon JE, Shy CM. Agricultural chemical use and congenital cleft lip and/or palate. Arch Environ Health 1981;36:213-221.

Hansen D, Lou HC, Olsen J. Serious life events and congenital malformations: A national study with complete follow-up. Lancet 2000;356:875-880.

Hanson JW, Myrianthopoulos NC, Harvey MA, Smith DW. Risks to the offspring of women treated with hydantoin anticonvulsant, with emphasis on the fetal hydantoin syndrome. J Pediatr 1976;89:662-668.

Hanson JW, Ardinger HH, DiLiberti J, et al. Effects of valproate on the fetus. Pediatr Res 1984;18:306A.

Hartsfield JK Jr, Hickman TA, Everett ET, Shaw GM, Lammer EJ, Finnell RA. Analysis of the EPHX1 113 polymorphism and GSTM1 homozygous null polymorphism and oral clefting associated with maternal smoking. Am J Med Genet 2001;102:21-24.

Hassler JA, Moran DJ. Effects of ethanol on the cytoskeleton of migrating and differentiating neural crest cells: Possible role in teratogenesis. J Craniofac Genet Dev Biol 1986;6(Suppl 2):129-136.

Hayes C, Werler MM, Willett WC, Mitchell AA. Case-control study of periconceptional folic acid supplementation and oral clefts. Am J Epidemiol 1996;143:1229-1234.

Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000;343:1608-1614.

Hollier LM, Leveno KJ, Kelly MA, MCIntire DD, Cunningham FG. Maternal age and malformations in singleton births. Obstet Gynecol 2000;96:701-706.

Holmberg PC, Hernberg S, Kurppa K, Rantala K, Riala R. Oral clefts and organic solvent exposure during pregnancy. 1982;50:371-376.

Hwang SJ, Beaty TH, Panny SR, Street NA, Joseph JM, Gordon S, McIntosh I, Francomano CA. Association study of transforming growth factor alpha (TGF-alpha) TaqI polymorphism and oral clefts: Indication of gene-environment interaction in a population-based sample of

infants with birth defects. Am J Epidemiol 1995; 141:629-636.

Irgens A, Kruger K, Skorve AH, Irgens LM. Birth defects and paternal occupational exposure. Hypotheses tested in a record linkage based dataset. Acta Obstet Gynecol Scand 2000;79:465-470.

Irgens A, Kruger K, Skorve AH, Irgens LM. Reproductive outcome in offspring of parents occupationally exposed to lead in Norway. Am J Ind Med 1998;34:431-437.

Itikala PR, Watkins ML, Mulinare J, Moore CA, Liu Y. Maternal multivitamin use and orofacial clefts in offspring. Teratology 2001;63:79-86.

Jaakkola JJ, Magnus P, Skrondal A, Hwang BF, Becher G, Dybing E. Foetal growth and duration of gestation relative to water chlorination. Occup Environ Med 2001 Jul;58(7):437-442.

Janssen PA, Rothman I, Schwartz SM. Congenital malformations in newborns of women with established and gestational diabetes in Washington State, 1984-1991. Paediatr Perinat Epidemiol 1996;10:52-63.

Johnston MC, Hunter WS. Cleft lip and/or palate in twins: Evidence for two major lip groups. Teratology 1989;39:461.

Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 1999;93:392-395.

Kallen B, Mastroiacovo P, Robert E. Major congenital malformations in Down syndrome. Am J Med Genet 1996;65:160-166.

Kallen B. Congenital malformations in twins: a population study. Acta Genet Med Gemellol (Roma) 1986;35:167-178.

Kallen BA, Robert E. Drinking water chlorination and delivery outcome-a registry-based study in Sweden. Reprod Toxicol 2000;14:303-309.

Khoury MJ, Becerra JE, d'Almada PJ. Maternal thyroid disease and risk of birth defects in offspring: a population-based case-control study. Paediatr Perinat Epidemiol 1989a;3:402-420.

Khoury MJ, Gomez-Farias M, Mulinare J. Does maternal cigarette smoking during pregnancy cause cleft lip and palate in offspring? Am J Dis Child 1989b;143:333-337.

Khoury MJ, Erickson JD, Cordero JF, McCarthy BJ. Congenital malformations and intrauterine growth retardation: a population study. Pediatrics 1988;82:83-90.

Khoury MJ, Weinstein A, Panny S, Holtzman NA, Lindsay PK, Farrel K, Eisenberg M. Maternal cigarette smoking and oral clefts: A population-based study. Am J Public Health 1987;77:623-625.

Ko CW, Hoffman HJ, Stick MJ, Wu Y, Bakewell JM. Recurrence risks for non-syndromic cleft lip and/or cleft palate (CL +/- P) using sibships in Missouri. Paediatr Perinat Epidemiol 2001;15:A19.

Kristensen P, Irgens LM, Andersen A, Bye AS, Sundheim L. Birth defects among offspring of Norwegian farmers, 1967-1991.Epidemiology 1997;8:537-544.

Lapunzina P, Lopez Camelo JS, Rittler M, Castilla EE. Risks of congenital anomalies in large for gestational age infants. J Pediatr 2002;140:200-204.

Lary JM, Paulozzi LJ. Sex differences in the prevalence of human birth defects: a population-based study. Teratology 2001;64:237-251.

Laumon B, Martin JL, Collet P, Bertucat I, Verney MP, Robert E. Exposure to organic solvents during pregnancy and oral clefts: a case-control study. Reprod Toxicol 1996;10:15-19.

Leck I, Lancashire RJ. Birth prevalence of malformations in members of different ethnic groups and in the offspring of matings between them, in Birmingham, England. J Epidemiol Community Health 1995;49:171-179.

Lieff S, Olshan AF, Werler M, Strauss RP, Smith J, Mitchell A. Maternal cigarette smoking during pregnancy and risk of oral clefts in newborns. Am J Epidemiol 19999;150:683-694.

Loffredo LC, Souza JM, Freitas JA, Mossey PA. Oral clefts and vitamin supplementation. Cleft Palate Craniofac J 2001;38:76-83.

Lorente C, Cordier S, Bergeret A, De Walle HE, Goujard J, Ayme S, Knill-Jones R, Calzolari E, Bianchi F. Maternal occupational risk factors for oral clefts. Occupational Exposure and Congenital Malformation Working Group. Scand

J Work Environ Health 2000a;26:137-145.

Lorente C, Cordier S, Goujard J, Ayme S, Bianchi F, Calzolari E, De Walle HE, Knill-Jones R. Tobacco and alcohol use during pregnancy and risk of oral clefts. Am J Public Health 2000b;90:415-419.

Lowry RB, Thunem NY, Silver M. Congenital anomalies in American Indians of British Columbia. Genet Epidemiol 1986;3:455-467.

Martinelli M, Scapoli L, Pezzetti F, Carinci F, Carinci P, Stabellini G, Bisceglia L, Gombos F, Tognon M. C677T variant form at the MTHFR gene and CL/P: A risk factor for mothers? Am J Med Genet 2001;98:357-360.

Martinez-Frias ML, Rodriguez-Pinilla E. Epidemiologic analysis of prenatal exposure to cough medicines containing dextromethorphan: No evidence of human teratogenicity. Teratology 2001;63:38-41.

Mastroiacovo P, Castilla EE, Arpino C, Botting B, Cocchi G, Goujard J, Marinacci C, Merlob P, Metneki J, Mutchinick O, Ritvanen A, Rosano A. Congenital malformations in twins: an international study. Am J Med Genet 1999;83:117-124.

Matte TD, Mulinare J, Erickson JD. Case-control study of congenital defects and parental employment in health care. Am J Ind Med 1993;24:11-23.

McIntosh GC, Olshan AF, Baird PA. Paternal age and the risk of birth defects in offspring. Epidemiology 1995;6:282-288.

Meadow SR. Congenital abnormalities and anticonvulsant drugs. Proc R Soc Med 1970;63:48-49.

Mili F, Edmonds LD, Khoury MJ, McClearn AB. Prevalence of birth defects among low-birth-weight infants. A population study. Am J Dis Child 1991;145:1313-1318.

Mills JL, Kirke PN, Molloy AM, Burke H, Conley MR, Lee YJ, Mayne PD, Weir DG, Scott JM. Methylenetetrahydrofolate reductase thermolabile variant and oral clefts. Am J Med Genet 1999;86:71-74.

Mitchell AA, Rosenberg L, Shapiro S, Slone D. Birth defects related to Bendectin use in pregnancy. I. Oral clefts and cardiac defects. JAMA 1981;245:2311-2314.

Mitchell LE, Murray JC, O'Brien S, Christensen K. Evaluation of two putative susceptibility loci for oral clefts in the Danish population. Am J Epidemiol 2001;153:1007-1015.

Moore LL, Singer MR, Bradlee ML, Rothman KJ, Milunsky A. A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. Epidemiology 2000;11:689-694.

Mulinare J, Erickson JD, James LM, et al. Does periconceptional use of multivitamins reduce the occurrence of birth defects? Am J Epidemiol 1995:141:S3.

Munger RG, Romitti PA, Daack-Hirsch S, Burns TL, Murray JC, Hanson J. Maternal alcohol use and risk of orofacial cleft birth defects. Teratology 1996;54:27-33.

Munger R, Romitti P, West N, et al. Maternal intake of folate, vitamin B-12, and zinc and risk of orofacial cleft birth defects. Am J Epidemiol 1997;145:S30.

Natsume N, Kawai T, Ogi N, Yoshida W. Maternal risk factors in cleft lip and palate: case control study. Br J Oral Maxillofac Surg 2000;38(1):23-25.

Nurminen T, Rantala K, Kurppa K, Holmberg PC. Agricultural work during pregnancy and selected structural malformations in Finland. Epidemiology 1995;6:23-30.

Orioli IM, Vieira AR, Castilla EE, Ming JE, Muenke M. Mutational analysis of the Sonic Hedgehog gene in 220 newborns with oral clefts in a South American (ECLAMC) population. Am J Med Genet 2002;108:12-15.

Orioli IM, Castilla EE. Epidemiological assessment of misoprostol teratogenicity. BJOG 2000;107:519-523.

Owens JR, Jones JW, Harris F. Epidemiology of facial clefting. Arch Dis Child 1985;60:521-524.

Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, Friesen MH, Jacobson S, Kasapinovic S, Chang D, Diav-Citrin O, Chitayat D, Nulman I, Einarson TR, Koren G. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies.

Teratology 2000;62:385-392.

Ramos-Arroyo MA. Birth defects in twins: study in a Spanish population. Acta Genet Med Gemellol (Roma) 1991;40:337-344.

Ramos-Arroyo MA, Rodriguez-Pinilla E, Cordero JF. Maternal diabetes: the risk for specific birth defects. Eur J Epidemiol 1992;8:503-508.

Rasmussen SA, Moore CA, Paulozzi LJ, Rhodenhiser EP. Risk for birth defects among premature infants: A population-based study. J Pediatr 2001;138:668-673.

Riley MM, Halliday JL, Lumley JM. Congenital malformations in Victoria, Australia, 1983-95: an overview of infant characteristics. J Paediatr Child Health 1998;34:233-240.

Rittler M, Liascovich R, Lopez-Camelo J, Castilla EE. Parental consanguinity in specific types of congenital anomalies. Am J Med Genet 2001;102:36-43.

Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA. Ambient air pollution and risk of birth defects in Southern California. Am J Epidemiol 2002;155:17-25.

Robert E, Vollset SE, Botto L, et al. Malformation surveillance and maternal drug exposure: The MADRE project. Int J Risk Safety Med 1994;6:75-118.

Rodriguez Pinilla E, Martinez Frias ML. Corticosteroids during pregnancy and oral clefts: A case-control study. Teratology 1998;58:2-5.

Romitti PA, Lidral AC, Munger RG, Daack-Hirsch S, Burns TL, Murray JC. Candidate genes for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype-environment interactions from a population-based case-control study of orofacial clefts. Teratology 1999;59:39-50.

Rosenberg L, Mitchell AA, Shapiro S, Slone D. Selected birth defects in relation to caffeine-containing beverages. JAMA 1982;247:1429-32.

Rosenberg L, Mitchell AA, Parsells JL, Pashayan H, Louik C, Shapiro S. Lack of relation of oral clefts to Diazepam use during pregnancy. N Engl J Med 1983;309:1282-1285.

Shaw GM, Croen LA, Curry CJ. Isolated oral cleft malformations: associations with maternal and infant characteristics in a California population. Teratology 1991;43:225-228.

Shaw GM, Lammer EJ, Wasserman CR, O'Malley CD, Tolarova MM. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. Lancet 1995;346:393-6.

Shaw GM, Wasserman CR, Lammer EJ, O'Malley CD, Murray JC, Basart AM, Tolarova MM. Orofacial clefts, parental cigarette smoking, and transforming growth factor-alpha gene variants. Am J Hum Genet 1996;58:551-561.

Shaw GM, Rozen R, Finnell RH, Todoroff K, Lammer EJ. Infant C677T mutation in MTHFR, maternal periconceptional vitamin use, and cleft lip. Am J Med Genet 1998a;80:196-198.

Shaw GM, Wasserman CR, Murray JC, Lammer EJ. Infant TGF-alpha genotype, orofacial clefts, and maternal periconceptional multivitamin use. Cleft Palate Craniofac J 1998b;35:366-70.

Shaw GM, Lammer EJ. Maternal periconceptional alcohol consumption and risk for orofacial clefts. J Pediatr 1999;134:298-303.

Shaw GM, Wasserman CR, O'Malley CD, Nelson V, Jackson RJ. Maternal pesticide exposure from multiple sources and selected congenital anomalies. Epidemiology 1999a;10:60-66.

Shaw GM, Nelson V, Todoroff K, Wasserman CR, Neutra RR. Maternal periconceptional use of electric bed-heating devices and risk for neural tube defects and orofacial clefts. Teratology 1999b;60:124-129.

Shaw GM, Carmichael SL, Nelson V. Congenital malformations in offspring of Vietnamese women in California, 1985-97. Teratology 2002;65:121-124.

Shiono PH, Kelbanoff MA, Berendes HW. Congenital malformation and maternal smoking during pregnancy. Teratology 1986;34:65-71.

Sohan K, Freer M, Mercer N, Soothill P, Kyle P. Prenatal detection of facial clefts. Fetal Diagn Ther 2001;16:196-199.

Sorensen HT, Czeizel AE, Rockenbauer M, Steffensen FH, Olsen J. The risk of limb deficiencies and other congenital abnormalities in children exposed in utero to calcium channel blockers. Acta Obstet Gynecol Scand

2001;80:397-401.

Spilson SV, Kim HJ, Chung KC. Association between maternal diabetes mellitus and newborn oral cleft. Ann Plast Surg 2001;47:477-481.

Stoll C, EUROCAT Working Group. Distribution of single organ malformations in European populations. Ann Genet 1995;38:32-43.

Stoll C, Dott B, Alembik Y, Roth MP. Evaluation of routine prenatal diagnosis by a registry of congenital anomalies. Prenat Diagn 1995;15:791-800.

Stoll C, Alembik Y, Dott B, Roth MP, Finck S. Evaluation of prenatal diagnosis by a registry of congenital anomalies. Prenat Diagn 1992;12:263-270.

Stoll C, Alembik Y, Dott B, Roth MP. Epidemiological and genetic study in 207 cases of oral clefts in Alsace, northeastern France. J Med Genet 1991;28:325-329.

Stoltenberg C, Magnus P, Lie RT, Daltveit AK, Irgens LM. Birth defects and parental consanguinity in Norway. Am J Epidemiol 1997;145:439-448.

Streissguth AP, Landesman-Dwyer S, Martin JC, Smith DW. Teratogenic effects of alcohol in humans and laboratory animals. Science 1980;209:353-361.

Tolarova M, Harris J. Reduced recurrance of orofacial clefts after periconceptional supplementation with high-dose folic acid and multivitamins. Teratology 1995;51:71-78.

Torfs CP, Christianson RE. Anomalies in Down syndrome individuals in a large population-based registry. Am J Med Genet 1998;77:431-438.

Van den Eeden SK, Karagas MR, Daling JR, Vaughan TL. A case-control study of maternal smoking and congenital malformations. Ped Perinatal Epidemiol 1990;4:147-55.

van Rooij IA, Wegerif MJ, Roelofs HM, Peters WH, Kuijpers-Jagtman AM, Zielhuis GA, Merkus HM, Steegers-Theunissen RP. Smoking, genetic polymorphisms in biotransformation enzymes, and nonsyndromic oral clefting: a gene-environment interaction. Epidemiology 2001;12:502-507.

Vinceti M, Rovesti S, Bergomi M, Calzolari E, Candela S, Campagna A, Milan M, Vivoli G. Risk of birth defects in a population exposed to environmental lead pollution. Sci Total Environ 2001;278:23-30.

Vrijheid M, Dolk H, Stone D, Abramsky L, Alberman E, Scott JE. Socioeconomic inequalities in risk of congenital anomaly. Arch Dis Child 2000;82:349-52.

Waller DK, Keddie AM, Canfield MA, Scheuerle AE. Do infants with major congenital anomalies have an excess of macrosomia? Teratology 2001;64:311-317.

Warkany J. Aminopterin and methotrexate: folic acid deficiency. Teratology 1978;17:353-357.

Werler MM, Hayes C, Louik C, Shapiro S, Mitchell AA. Multivitamin supplementation and risk of birth defects. Am J Epidemiol 1999;150:675-682.

Werler MM, Lammer EJ, Rosenberg L, Mitchell AA. Maternal cigarette smoking during pregnancy in relation to oral clefts. Am J Epidemiol 1990;132:926-32.

Werler MM, Lammer EJ, Rosenberg L, Mitchell AA. Maternal alcohol use in relation to selected birth defects. Am J Epidemiol 1991;134:691-8.

Werler MM. Teratogen update: Smoking and reproductive outcomes. Teratology 1997;55:382-388.

Wyszynski DF, Beaty TH. Review of the role of potential teratogens in the origin of human nonsyndromic oral clefts. Teratology 1996;53:309-317.

Yoon PW, Merz R, Forrester M, et al. The effect of maternal race on oral clefts in Hawaii. Am J Epidemiol 1997;145:S3.

Zackai EH, Mellman WJ, Neiderer B, Hanson JW. The fetal trimethadione syndrome. J Pediatr 1975;87:280-284.

Zhang J, Cai WW. Association of the common cold in the first trimester of pregnancy with birth defects. Pediatrics 1993;92:559-563.

Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and*

limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information.

This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.